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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,437	12/31/2003	Kwen-Jen Chang	4080-130	8959

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,437	CHANG ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-7,9-13,15-19,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14,20-28 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/4/05, 05/06/06, 12/31/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, the Group II along with 4-{(2R,5S)-4-[(R)-(4-diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl]benzoic acid is acknowledged. Claims 8, 14, 20-28 and 31-40 read on the elected species.

Claims 1-7, 9-13, 15-19 and 29-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Information Disclosure Statement

2. Acknowledgement is made of applicant's submitting of the information disclosure statement (IDS) on 05/06/04, 10/04/05 and 06/06/06. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement (IDS) has been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 8, 14, 20-28 and 31-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific ischemic damage (e.g., myocardial infarction) or reducing ischemic damage in cardiac tissue with the administration of 4-{(2R,5S)-4-[(R)-(4-diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl]benzoic acid, does not reasonably provide enablement for "reducing ischemic damage", "protecting against ischemia and reperfusion injury" or "effectuating ischemic

preconditioning of cardiac tissue" with the administration of compound of the formula (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention (particularly claims 20, 22, 24, 31-40) is related to a method of protecting or preventing (Websters II Dictionary defines the term "prevent" as "anticipate or counter in advance, to keep from happening") ischemic damage or ischemic heart disease progression administering a compound of the formula (1) or (2) prior to the onset of an ischemic event or to the subject at potential risk of having ischemia.

The specification disclose that ischemic preconditioning is a phenomenon, widely demonstrated in many species, including man, whereby the myocardium is protected from a major ischemic event by prior brief periods of ischemia or hypoxia followed by reperfusion or reoxygenation (page 2, lines 25-30). Since the interpretation of the instantly claimed invention (claims 33-37) allows for the inclusion of protection of heart from the ischemic event, this

invention is grouped together with the protective or prophylactic utility of the claims 31-32 and 38-40.

In addition, since the interpretation of the instantly claimed invention (claims 8, 14 and 20) allows for the inclusion of the administration of said composition prior to the onset of ischemia, as a preventing regime to prevent disease progression in an individual in the symptomatic phase of ischemic heart disease or to effectuate a protective or corrective cardiac response, the invention (claims 8, 14, 20, 22, 24-28) is grouped together with the protective or prophylactic utility of the claims 31-32 and 38-40.

There are no known compounds of similar structure which have been demonstrated to prevent a disease or condition mediated by ischemic damage or ischemia and reperfusion injury. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "magic bullet" is contrary to our present understanding of pharmacology. For example, there is no known cure for a disease or condition of platelet aggregation such as myocardial infarction, coronary heart disease and stroke. The true fact of the state of the art is illustrated succinctly in the "NIH Heart Disease & Stroke Research: Fact Sheet" (American Heart Association, 2004); "Cardiovascular Disease: Treatment for Stroke", Stanford Hospital & Clinics, 2003; "Heart Disease", Charlotte E. Grayson, WebMD, 2004; "Acute Congestive Heart Failure", Thomas N. Levin, Postgraduate Medicine, Vol. 101, No. 1, 1997). Thus, it is beyond the skill of pharmacologists today to get an agent to be cure or completely eliminate the condition encompassed by the claimed invention.

The relative skill of those in the pharmaceutical art is high. The unpredictability of the pharmaceutical art is very high. As stated above, applicants have not provided any competent

evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The claims are very broad. The scope of the instant claims encompasses prevention (complete thwarting or warding off illness or total elimination or eradication of disease) or treatment of multiple complex disorders that may have unrelated manifestations including coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism and etc...

The instant specification provides assays in vitro and discloses that said compound, namely compound 1 exhibits delta opioid agonist activity (Example 5) and is capable of reducing the infarct size or the necrosis of infarct heart tissue in rat (Examples 8 and 9).

Although it is true that ischemia or ischemia and reperfusion may be involved in pathophysiology of multitude of diseases, for example coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease,

pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism, it is not know yet that a single underlying mechanism ties together all of the seemingly unrelated manifestations. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of the claimed diarylmethylpiperazine compound delta opioid agonist.

As discussed above, although the specification describes working examples of using compound 1 having delta opioid receptor agonist for reducing ischemic damage to the heart tissue (intended treatment of myocardial infarction), there is no demonstrated correlation that the tests and results apply to the prevention or treatment of all of the disorders embraced by the instant claims. In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent method claim 8 recites "the composition according to claim 1". Although the diarylmethylpiperazine compound of the formula (1) is recited in claim 1, it is considered that the meaning of the independent claim 8 should be clear from the wording of the claim alone. Thus, the claim without the recitation of the structure of the diarylmethylpiperazine compound of the formula (1) leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 8, 14, 20-23, 27-28, 33-34 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US 7030124 B2) in view of Schultz et al. (US 6103722).

Chang teaches diarylpieprazine compounds of formula (1) including compounds (i), (vii), (viii), (xii) and (xiii) or pharmaceutically acceptable ester (including carboxylic acid esters of the hydroxyl group in the compounds of formula (1)) or salt thereof that is useful as delta opioid receptor agonist (column 1, lines 17-22 and column 3, line 50 thru column 8, line 65), wherein said compound is formulated in various dosage formulation including oral, rectal, topical, sub-lingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic and intra-uterine forms (column 9, lines 6-12), and wherein said compound is administered in dosage range of 10 micrograms to 100 milligrams per kg body weight per day, preferably in the range of 50 microgram to 75 mg/kg per day and most preferably in the range of 100 microgram to 50 mg/kg per day over two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day (column 25, line 53 thru column 2, line 5) for the treatment of depression. Chang discloses that Ar^2 can be 6-member carbocyclic with carbon atom thereof a substitute X, wherein X is selected from the group consisting of hydrogen, halogen, hydroxy and alkoxy (column 3, lines 19-42; column 22, lines 34-37).

Schultz teaches use of delta opioid receptor agonist including diarylmethylpiperazine compound such as BW373U86 and SNC80 as a cardioprotective agent for reducing ischemic damage or ischemia and reperfusion injury (e.g., angina pectoris, myocardial infarction and

restenosis) or blocking ischemic preconditioning in mammal including human (abstract; column 1, lines 20-25; column 3, line 61 thru column 4, line 37; column 7, lines 8-12; Figures) wherein said delta opioid receptor agonist is administered prior, during or after the ischemic event or ischemia or surgery (column 12, lines 53-57; Example 1 and 2), and wherein said compound is administered in various dosage forms including oral or injection per day, either at once or spread over several times (column 12, lines 58-67).

The teaching of Chang differs from the claimed invention in (i) the selection of the specific species, namely 4-{(2R,5S)-4-[(R)-(4-diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl]benzoic acid and the administration of said compound to a patient having or at risk of having ischemia or ischemic event to reduce ischemic damage to the human heart, block ischemic preconditioning (claims 8, 14, 20-28 and 31-40), and (ii) the administration of said compound in "multiple times currently with the onset of an ischemic event" (claim 20) and "after the onset of an ischemic event" (claim 23).

To incorporate such teaching into the teaching Chang, would have been obvious in view of Schultz who teaches the utility of using delta opioid receptor agonist such diarylmethylpiperazine compounds as a cardioprotective agent for reducing ischemic damage or ischemia and reperfusion injury to human or human heart, or blocking ischemic preconditioning and the administration of delta opioids in various dosage forms including oral and dosage administration regimen (e.g., per day, at once or spread over several times).

It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those of the

claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties, thus, the same use as the genus as a whole.

Furthermore, one having ordinary skill in the art would have expected as taught by Schultz that the drugs having diarylmethylpiperazine core structure compound having delta opioid receptor agonist is useful in the therapeutic treatment of ischemia, ischemic damage or blocking ischemic preconditioning.

With respect to the selection of the specific administration regimen (particularly prior, during or after the onset of an ischemic event) and dosage forms (particularly oral and other forms including parenteral, rectal, topical, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, etc...), those of ordinary skill in the art would have been readily determined dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage or administration regimen for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the administration regimen and dosage information disclosed in the Chang and Schultz.

With respect to "non-analgesic diarylmethylpiperazine compound of the formula" (claims 14, 20-28",

Since such property or characteristic must be expected feature of said diarylmethylpiperazine within the prior art dosage range, the references in combination makes obvious the instant invention.

Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

6. Claims 24-26, 31-32 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US 7030124 B2) in view of Schultz et al. (US 6103722), and further in view of Applicant's admission of the prior art (page 9, lines 5-7).

The modified teaching of Chang includes all that is recited in claims 24-26, 31-32 and 35-37 except the use of second agent (claims 24-26, 31-32 and 35-37), namely as nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists, aspirin (claims 25 and 36) and arginine hydrochloride (claim 32) and the administration of the second compound contemporaneously with the diarylmethylpiperazine compound (claims 26 and 37).

Applicant's admission of the prior art teaches the use of nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists and aspirin as known cardiac therapeutic agent.

Oeltegen is being supplied a supplemental reference to demonstrate the state of art knowledge in using arginine hydrochloride as a cardiac therapeutic agent (column 3, lines 65-67 and claim 8).

Above references in combination make clear that the diarylmethylpiperazine compound and the second agent (e.g., nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists and aspirin and arginine)

have been individually used for the treatment of ischemia or ischemic damage to heart. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

With respect to the determination of the specific administration regimen, namely "administered contemporaneously with the diarylmethylpiperazine compound", those of ordinary skill in the art would have been readily determined concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate administration regimen for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, absence evidence to the contrary.

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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